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A REVIEW: METHODS FOR ENHANCING BIOAVAILABILITY OF DRUG

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Abstract:

Bioavailability is a term used by several branches of scientific study to describe the way chemicals are absorbed by humans and other animals. Bioavailability was once strictly ascribed to pharmacology. Examining a substance's bioavailability in pharmacological studies helps to determine dosages of particular medications. A bioavailability measurement of a medication, when it reaches circulation in the body, describes aspects like absorbency and half-life. It can evaluate medication delivery as well. Bioavailability can be improved by imparting various changes to new chemical entity (NCE) by various methods like SMEDDS technology, by Selective adsorption on insoluble carrier technique, by molecular encapsulation with cyclodextrins, by Nanosuspensions formation for enhancing the dissolution of poorly soluble drugs and also by the conjugation of proteins. Intravenous administrations of medications are considered to have 100% bioavailability because they do not pass through the stomach. They are immediately in the circulatory system. However, other medications administered at the same time may reduce the effects of an intravenous administration and affect its bioavailability.

Key words: Bioavailability, enhancement of bioavailability, cyclodextrine, SMEDDS.

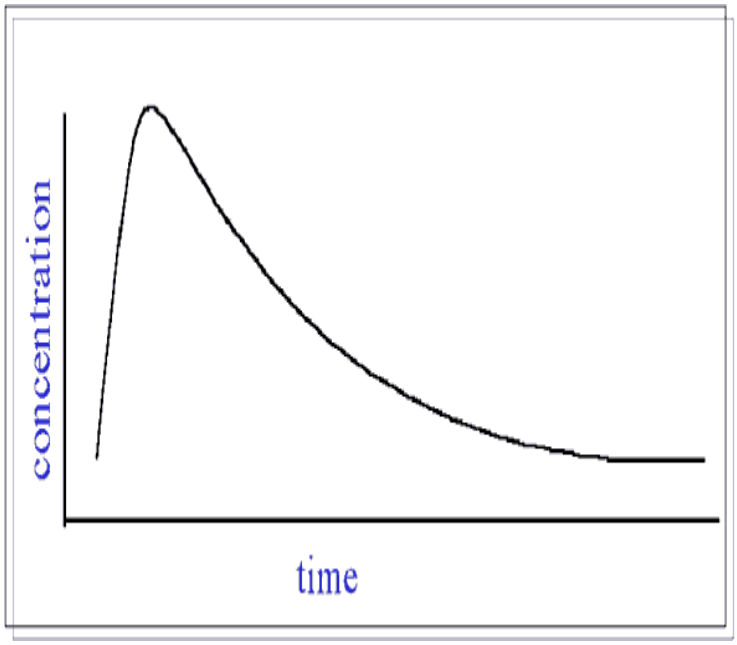
I. Introduction

A. Bioavailability

Definition: Bioavailability is a measurement of the rate and extent of a therapeutically active drug that reaches the systemic circulation and is available at the site of action. It is denoted by the letter F.[1]

Or

Is the degree of ability to be absorbed and ready to interact in organism metabolism (U.S.EPA) [1]



Bioavailability = Rate and Extent of Absorption

a. Absolute bioavailability

Absolute bioavailability compares the bioavailability (estimated as the area under the curve, or AUC) of the active drug in systemic circulation following non-intravenous administration (i.e., after oral, rectal, transdermal, subcutaneous, or sublingual administration), with the bioavailability of the same drug following intravenous administration. It is the fraction of the drug absorbed through non-intravenous administration compared with the corresponding intravenous administration of the same drug. The comparison must be dose normalized if different doses are used; consequently, each AUC is corrected by dividing the corresponding dose administered.

In order to determine absolute bioavailability of a drug, a pharmacokinetic study must be done to obtain a plasma drug concentration vs time plot for the drug after both intravenous (IV) and non-intravenous administration. The absolute bioavailability is the dose-corrected area under curve (AUC) non-intravenous divided by AUC intravenous. For example, the formula for calculating F for a drug administered by the oral route (p. o) is given below.

$$F = \frac{[AUC]_{po} * dose_{IV}}{[AUC]_{IV} * dose_{po}}$$

Therefore, a drug given by the intravenous route will have an absolute bioavailability of 1 (F=1) while drugs given by other routes usually have an absolute bioavailability of less than one. If we compare the two different dosage forms having same active ingredients and compare the two drug bioavailability is called comparative bioavailability. Although knowing the true extent of systemic absorption (referred to as absolute bioavailability) is clearly useful, in practice it is not determined as frequently as one may think. The reason for this is that its assessment requires an intravenous reference, that is, a route of administration that guarantees that all of the administered drug reaches the systemic circulation. Such studies come at considerable cost, not least of which is the necessity to conduct preclinical toxicity tests to ensure adequate safety, as well as there being potential problems due to solubility limitations.

There is no regulatory requirement to define the intravenous pharmacokinetics or absolute bioavailability however regulatory authorities do sometimes ask for absolute bioavailability information of the extra vascular route in cases in which the bioavailability is apparently low or variable and there is a proven relationship between the pharmacodynamics and the pharmacokinetics at therapeutic doses. In all such cases, to conduct an absolute bioavailability study requires that the drug be given intravenously.

Intravenous administration of a developmental drug can provide valuable information on the fundamental pharmacokinetic parameters of volume of distribution (V) and clearance (CL).[2,3]

b. Relative bioavailability

This measures the bioavailability (estimated as area under the curve, or AUC) of a certain drug when compared with another formulation of the same drug, usually an established standard, or through administration via a different route. When the standard consists of intravenously administered drug, this is known as relative bioavailability.

$$relative\ \ bioavailability = \frac{[AUC]_A * dose_B}{[AUC]_B * dose_A}$$

0.05 level of significance For FDA approval , a generic manufacturer must show that the 90% confidence interval for the ratio of the mean response (usually AUC and Cmax) of its product to that of the "Brand Name drug" is within the limits of 0.8 to 1.25 at the 0.05 level of significance.[4.3]

For what:

- Poor aqueous solubility by novel co grinding method using Poor stability
- Inadequate water-soluble polymer
- Partition coefficient
- Extensive presystemic metabolism.[5]

II. Major approaches in overcoming the bioavailability

1. Pharmaceutical approach

   Formulation, Process, Physicochemical Modifications.

2. Pharmacokinetic approach

   Chemical Modification.

3. Biologic approach

Rout change, oral to parenteral.[5]

III. Methods for Enhancing Bioavailability of Drug

1. Micronisation

- Reduces practical size to Sub-micron (1-10 micron meter)

By

- Milling and grinding
- Crushing and cutting

Micronization is the process of reducing the average diameter of a solid material's particles. Usually, the term micronization is used when the particles that are produced are only a few micrometers in diameter. However, modern applications (usually in the pharmaceutical industry) require average particle diameters of the nanometer scale.[6]

a) Traditional techniques

Traditional micronization techniques are based on friction to reduce particle size. Such methods include milling and grinding. A typical industrial mill is composed of a cylindrical metallic drum that usually contains steel spheres. As the drum rotates the spheres inside collide with the particles of the solid, thus crushing them towards smaller diameters. In the case of grinding, the solid particles are formed when the grinding units of the device rub against each other while particles of the solid are trapped in between.

Methods like crushing and cutting are also used for reducing particle diameter, but produce more rough particles compared to the two previous techniques (and are therefore the early stages of the micronization process). Crushing employs hammer-like tools to break the solid into smaller particles by means of impact. Cutting uses sharp blades to cut the rough solid pieces into smaller ones.[7]

b) Modern techniques

Modern methods use supercritical fluids in the micronization process. The most widely applied techniques of this category include the RESS process (Rapid Expansion of Supercritical Solutions), the SAS method (Supercritical Anti-Solvent) and the PGSS method (Particles from Gas Saturated Solutions).[4,8]

In the case of RESS, the supercritical fluid is used to dissolve the solid material under high pressure and temperature, thus forming a homogeneous supercritical phase. Thereafter, the solution is expanded through a nozzle and small particles are formed. At the rapid expansion point right at the opening of the nozzle there is a sudden pressure drop that forces the dissolved material (the solid) to precipitate out of the solution. The crystals that are instantly formed enclose a small amount of the solvent that, due to the expansion, changes from supercritical fluid to its normal state (usually gas), thus breaking the crystal from inside-out. At the same time, further reduction of size is achieved while the forming and breaking crystals collide with each other at the vicinity of the nozzle. The particles that are formed this way have a diameter of a few hundreds of nanometers.[8]

In the SAS method, the solid material is dissolved in an organic solvent and a supercritical fluid is then also forced by means of pressure to dissolve in the system. In this way, the volume of the system is expanded, thus lowering the density, and therefore also the solubility of the material of interest is decreased. As a result, the material precipitates out of the solution as a solid with a very small particle diameter.[8]

In the PGSS method the solid material is melted and the supercritical fluid is dissolved in it, like in the case of the SAS method. However, in this case the solution is forced to expand through a nozzle, and in this way nanoparticles are formed.

In all three methods described, the effect that causes the small diameter of the solid particles is the super saturation that occurs at the time of the particle formation, like it was described in more detail in the case of the RESS process. The PGSS method has the advantage that because of the supercritical fluid, the melting point of the solid material is reduced. Therefore, the solid melts at a lower temperature than the normal melting temperature at ambient

pressure. In addition, all these new techniques do not demand long processing times, like in the case of the traditional methods. As a result, they are thought to be more appropriate when thermo-labile materials need to be processed (like pharmaceuticals and foodstuff ingredients).[8,4,3]

Examples:

Progesterone can be micronized by making very tiny crystals of the progesterone. Micronized progesterone is manufactured in a laboratory from plants. It is available for use as HRT, infertility treatment, treat progesterone deficiency treatment, including dysfunctional uterine bleeding in premenopausal women. Compounding pharmacies can supply micronized progesterone in sublingual tablets, oil caps, or transdermal creams.[8,4]

2. Improvement of dissolution characteristics

A novel co grinding method for improving dissolution characteristics of poorly water-soluble drugs was developed. A co ground mixture of nifedipine (NP)-polyethylene glycol 6000-hydroxypropylmethyl cellulose system prepared in the presence of small amount of water showed remarkable effect with respect to NP dissolution and its apparent solubility. Although the performance of the co ground mixture was superior to that of spray-dried powder with the same composition, the X-ray diffraction pattern indicated the mixture did not change to amorphous state. In addition, the transmission electron microscopy revealed that NP seemed to exist in coacervate-like fine particles (50–200 nm) in water. This co grinding method was also effective for other poorly water-soluble drugs such as griseofluvin and indomethacin. Some drug–polymer interactions through hydroxypropoxyl groups seemed to participate in the mechanism of the improvement of dissolution characteristics, because the content of the functional group affected the extent of solubility-enhancing effect. Furthermore, the addition of small amount of water in co grinding was especially effective, because it promoted the interactions. The co ground mixture showed the same plasma concentration as NP solution of PEG 400 when it was orally administered to beagle dogs. From these results, it is clear that the present co grinding method is very effective for improvement of bioavailability of poorly water-soluble drugs.[9,10]

3. **Use of salt form**

- Improve solubility & dissolution
- Alkali metal salt of acidic drugs like penicillin & strong acid salt of basic drugs like atropine more water soluble than parent drug [1,5]

4. **Alteration of pH of the drug microenvironment**

- In salt formation & buffer addition

E.g: Buffered Aspirin tablets.[5,8]

5. **Use of metastable polymorphs**

E.g. : Chloramphenicol-B more soluble than A & C form [5,11]

6. **Solute-solvant complexation**

- Solvates of drug with organic solvents (pseudopoly morphs) have greater aqueous solubility than hydrates / original drug
- Freezing drying solute with organic solvant ie solvate
- Result in particle of submicron range

E.g.: 1:2 Griseofulvins -benzene solvate[1,5]

7. **Solvant deposion**

Nifedipine poor aqueous soluble drug in alcohol & deposited on inert, hydrophilic matrix on starch or CMC by solvent evaporation.[4,5]

8. **Selective adsorption on insoluble carrier**

Bentonite highly active adsorbent enhances dissolution rate of poorly soluble griseofulvin, indomethacin & prednisone by maintaining conc. gradient at its maximum

Mainly due to:

Weak bonding

Hydration and swelling [5,12]

8. Lipidic Formulations

Liquid and semi-solid filled hard capsule formulations are also ideally suited to compounds with low aqueous solubility, poor permeability and consequently low or variable bioavailability. Formulations which increase the solubility of the active or indeed present the drug as a solution can have a significant impact on the bioavailability of such drugs. Lipidic vehicles are generally well absorbed from the GI tract and in many cases this approach can significantly improve the oral bioavailability compared with administration of the solid drug substance. Encap has expertise in the use of self-emulsifying vehicles and has developed a number of self-emulsifying drug delivery systems (SEDDS) and self-microemulsifying drug delivery systems (SMEDDS) for the oral administration of drugs with poor water solubility. These are formulations which form emulsions or micro emulsions spontaneously on contact with aqueous media. An example of a marketed product that uses a SMEDDS type formulation is Neoral (Novartis) for oral administration of cyclosporine. In addition, Encap can offer the possibility to explore formulation screening for this type of formulation using Gattefosse kits. Encap have experience of a wide range of functional 'bioavailability enhancer' excipients which are fully approved from a Regulatory perspective and include the screening of such excipients during pre-formulation studies. [5]

9. Solid solutions

A formulation strategy for poorly soluble drugs is the use of solid solutions, which are molecular dispersions of the drug molecules in a polymer matrix. This conversion of the drug into the amorphous state produces material which dissolves more rapidly than the corresponding crystalline drug substance. The incorporation of the drug substance into hydrophilic polymeric materials such as polyvinylpyrollidone (PVP) and polyethylene glycol (e.g. PEG6000) can produce additional solubility enhancing effects.

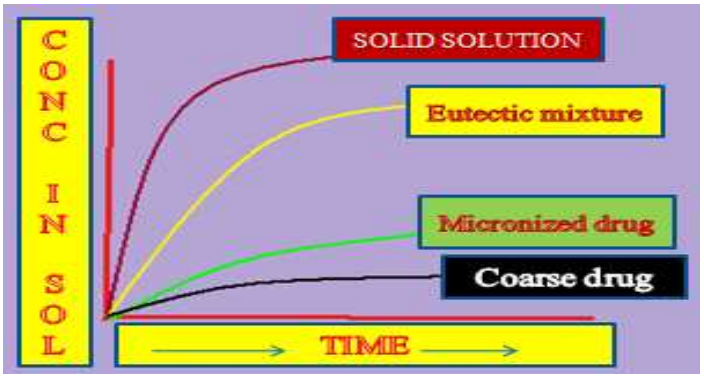
Solid solutions can be prepared by dissolving the drug and the polymer in a suitable volatile solvent. On removing the solvent (by spray drying) an amorphous drug/polymer complex is formed. In some cases it is possible to dissolve the

drug in the molten polymer and fill directly into hard capsules. On cooling, the drug is entrapped in an amorphous state within the water-soluble matrix.

In many cases, improvements in drug dissolution and bioavailability can also be achieved using dispersions or suspensions of drugs in appropriate vehicles which are suitable for filling into hard shell capsules.[5]

Three means for reducing particle size in submicron range

1. Solid solution
2. Eutectic mixture
3. Solid dispersion



10. Eutectic mixtures

Paracetamol-urea, griseofulvin-urea, griseofulvin-succinic acid etc.

Cannot be applied to:

1. Drugs which fails to crystallize from mixed melt,
2. Thermo labile drugs
3. Carriers such as succinic acid that decompose at it's melting point
4. Solid dispersion [5,13]

- Melt extrusion

17β-Estradiol hemihydrates (17β-E2) are a poorly water-soluble drug. Physical methods for improving the solubility and dissolution rate, e.g. micronization, have certain inherent disadvantages. The method of choice in this study, melt extrusion, proved to overcome many of the shortcomings of conventional methods. Different compositions of excipients such as PEG 6000, PVP (Kollidon® 30) or a vinylpyrrolidone-vinyl acetate-copolymer (Kollidon® VA64) were used as polymers and Sucroester® WE15 or Gelucire® 44/14 as additives during melt extrusion. The solid dispersions resulted in a significant increase in dissolution rate when compared to the pure drug or to the physical mixtures. For example, a 30-fold increase in dissolution rate was obtained for a formulation containing 10% 17β-E2, 50% PVP and 40% Gelucire® 44/14. The solid dispersions were then processed into tablets. The improvement in the dissolution behavior was also maintained with the tablets. The USP XXIII requirement for estradiol tablets reaching greater than 75% drug dissolved after 60 min was obtained in this investigation.[5,14]

11. Molecular encapsulation with cyclodextrins

Cyclodextrins are cyclic oligosaccharides with a hydrophilic outer surface and a somewhat lipophilic central cavity. Cyclodextrins are able to form water-soluble inclusion complexes with many lipophilic water-insoluble drugs. In aqueous solutions drug molecules located in the central cavity are in a dynamic equilibrium with free drug molecules. Furthermore, lipophilic molecules in the aqueous complexation media will compete with each other for a space in the cavity. Due to their size and hydrophilicity only insignificant amounts of cyclodextrins and drug/cyclodextrin complexes are able to penetrate into lipophilic biological barriers, such as intact skin. In general, cyclodextrins enhance topical drug delivery by increasing the drug availability at the barrier surface. At the surface the drug molecules partition from the cyclodextrin cavity into the lipophilic barrier. Thus, drug delivery from aqueous cyclodextrin solutions is both diffusion controlled and membrane controlled. It appears that cyclodextrins can only enhance topical drug delivery in the presence of water.[2,5,15]

12. Nanosuspensions for enhancing the dissolution of poorly soluble drugs

The capability of 0.5% polycarbophil cysteine conjugate (PCP-Cys) to reduce 0.02% oxidized glutathione (GSSG) was evaluated via iodometric titration in aqueous solution. Glutathione in its reduced form (GSH; 0.1%-0.4%) and in combination with 0.5% PCP-Cys were tested for their permeation enhancement of sodium fluorescein (NaFlu) and fluorescence labeled bacitracin (bac-FITC) used as paracellular markers. Permeation studies across guinea pig duodenum were carried out in Using-type chambers. Opening of the tight junctions was additionally monitored by transepithelial electrical resistance (TEER) measurements.[5,16]

13. Super Saturation

Permeation enhancement of ibuprofen from supersaturated solutions formed using the co solvent technique was investigated using silicone as a model membrane. Hydroxpropyl methyl cellulose and hydroxpropyl-β-cyclodextrin were used to stabilize the supersaturated states. Physical stability studies showed best results for low drug concentrations in a 40:60 propylene glycol/water co solvent system. Variations in flux across model silicone membranes from saturated solutions were observed as the PG content was increased. The flux of IBU increased with the degree of saturation for solutions prepared in a 40:60 PG/water co solvent mixture. HPMC and CD were found to be effective in enhancing the stability of supersaturated solutions of IBU.[17]

14. The conjugation of proteins

With polyethylene glycol and other polymers altering properties of proteins to enhance their therapeutic potential

The development of protein drugs for therapeutic purposes using recombinant DNA technology has generated a great deal of interest in methods of enhancing their delivery. One method of improving the delivery of proteins, and thereby increasing their therapeutic index, is covalent conjugation to polymers. This paper discusses polymers which are suitable for conjugation, methods of conjugation, the properties of polymer-protein conjugates and possibilities for designing drug delivery systems using these conjugates. The properties of protein-polymer conjugates include a

dramatic increase in bioavailability, decreased immunogenicity, and enhanced solubility and stability. These altered properties improve the delivery and efficacy of proteins and impart flexibility to their clinical usage.[18]

15. Self-emulsifying drug delivery systems (SEDDS)

The goals of our investigations are to develop and characterize self-emulsifying drug delivery systems (SEDDS) of coenzyme Q_{10} (CoQ_{10}), using polyglycolyzed glycosides' (PGG) as emulsifiers and to evaluate their bioavailability in dogs. Solubility of CoQ_{10} was determined in various oils and surfactants. SEDDS consisted of oil, a surfactant and a co surfactant. Four types of self-emulsifying formulations were prepared using two oils (Myvacet 9-45 and Captex-200), two emulsifiers (Labrafac CM-10 and Labrasol) and a co surfactant (lauroglycol). In all the formulations, the level of CoQ_{10} was fixed at 5.66% w/w of the vehicle. The in vitro self-emulsification properties and droplet size analysis of these formulations upon their addition to water under mild agitation conditions were studied. Pseudo-ternary phase diagrams were constructed identifying the efficient self-emulsification region. From these studies, an optimized formulation was selected and its bioavailability was compared with a powder formulation in dogs. Medium chain oils and Myvacet 9-45 provided higher solubility than long chain oils. Efficient and better self-emulsification processes were observed for the systems containing Labrafac CM-10 than formulations containing Labrasol. Addition of a co surfactant improved the spontaneity of self-emulsification. From these studies, an optimized formulation consisting of Myvacet 9-45 (40%), Labrasol (50%) and lauroglycol (10%) was selected for its bioavailability assessment. A two-fold increase in the bioavailability was observed for the self-emulsifying system compared to a powder formulation. SEDDS have improved the bioavailability of CoQ_{10} significantly. The data suggest the potential use of SEDDS to provide an efficient way of improving oral absorption of lipophilic drugs.[19]

Conclusion:

We conclude from the bioavailability study that conc of drug in blood increased to optimum level in the therapeutic window .By reducing the dose and enhancing the absorption of drug in to the blood through GIT. In each technology drug solubility and permeability is the main criteria for enhancing the bioavailability.

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